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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/700,264 | 11/03/2003 | John Byrd | 18525-04052 | 3693 |

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| EXAMINER | |
|---|---|
| YAO, LEI | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/700,264 | BYRD ET AL. | |
| | Examiner | Art Unit | |
| | Lei Yao, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *13-15 and 23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/13/04, 8/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's election of group II (claims 1-12 and 16-22), a method for predicting a patient with CLL to response to treatment with rituximab by analyzing the cell having abnormalities of deletion in chromosome by FISH in paper filed 1/13/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-30 are pending. Claims13-15 and 23-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1-12 and 16-22 will be examined on the merits.

### Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 4/13/06 and 8/24/05 are/is considered by the examiner and initialed copies of the PTO-1449 are enclosed.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness.

1. Claims 1-4, 6-7, and 16-17, 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golay et al., (Blood, vol 98, page 3383-9) in view of Hogan et al., (Cancer genet cytogenet, vol 110, page 77-81, 1999), Fongeca et al., (Leukemia, vol 15, page 981-6, 2001), Witzig et al., (Leukemia and lymphoma, vol 14, page 447-451, 1993), and Catovsky D (Hematol Cell Ther, vol 39, page S5-S11, 1997).

The set of the claims is drawn to a method for predicting a patient with chronic lymphocyte leukemia (CLL), who **responds to** treatment comprising Rituximab (anti-CD20 antibody) by analyzing the cells having deletion in chromosome by FISH.

Golay et al., teach that a method of determining the susceptibility of a patient with chronic lymphocyte leukemia (CLL) to Rituximab. Golay et al., teach that the levels of CD20 expression in CLL cells determine the susceptibility to the response to Rituximab (page 3386, col 1, para 2 and figure 8). Golay et al., teach that Rituximab-mediated lysis of CLL cell depends primarily on the levels of expression of CD20 molecule on the cells (page 3386, col 1, para 1). Golay et al., also teach that Rituximab lysis of CLL cells is correlated highly significantly with number of CD20 molecules per cells and these results could be applied to analyze the role of CD20 expression in the in vivo response of different patients to rituximab (page 3388, col 2, line5-15).

Golay et al., do not teach the relationship between abnormalities of chromosome and expression of CD20 and do not teach FISH and probes for detection of abnormalities of chromosome.

Hogan et al., teach that all the CD20 positive CLL cells have 13q14 deletion, which is detected by FISH using probe Locus specific probes (LSI) D13S319 (Rb1 D13S319, abstract, line 7; page 78, col 2, para 1,). LSI 13 is Rb as evidenced by Fongeca et al., (Leukemia, vol 15, page 981-6, 2001).

Witzig et al., teach that the CD20 positive CLL cells have Trisomy 12 detected by FISH using a probe specific for centromere of chromosome 12 (CEP 12).

Catovsky D teaches that chromosome deletion 17p13.1 results in p53 deletion and dysfunction, which is associated with CLL and frequent failure to respond to therapy (page S9, col 1, para 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method for predicting the response of a patient with CLL treated with an agent binding to CD20 comprising Rituximab. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Hogan et al., Witzig et al., and Catovsky D to the teaching of Golay et al., to predict the response of a patient with specific type of CLL to a treatment with antibody to CD20 (Rituximab) after analyzing the CLL with the abnormalities of chromosome, (deletion of chromosome) because both Hogan et al., and Witzig et al., have shown that CD20 positive CLL cells have 13q14 deletion and Trisomy 12, which could be detected by FISH using probe D13S319 or probe CEP 12 and because Catovsky D has shown that deletion 17p13.1 only result in p53 deletion not others. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to predict whether a patient can respond to the treatment of Rituximab after knowing the type of chromosome deletion because Golay et al., have shown that the patient, who responds to the Rituximab treatment, has malignant leukemic CD20 positive B cells.

2. Claims 1-8 and 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golay et al., (Blood, vol 98, page 3383-9), Catovsky D (Hematol Cell Ther, vol 39, page S5-S11, 1997), Hogan et al., (Cancer genet cytogenet, vol 110, page 77-81, 1999) and Witzig et al., (Leukemia and lymphoma, vol 14, page 447-451, 1993) further in view of Morrison (US Patent Application Publication, US 2003/0087248, effective filing date Feb, 20, 2001) and Stilgenbauer et al., (Blood, vol 94, page 3262-4, 1999).

The teachings of Golay et al., Hogan et al., Witzig et al., and Catovsky D are set forth above.

Golay et al., Hogan et al., Witzig et al., and Catovsky do not teach detecting deletion of 17p13.1 of chromosome 17 and 11q22-q23 of chromosomal 12 by FISH using the probe LSI 53 and ATM probe.

Morrison et al., teach polynucleotide probe **LSI p53**, which is complementary to and hybridize with target region 17p13.1 of chromosomal 17.

Stilgenbauer et al., teach **ATM probe** for detecting a deletion in 11q22-q23.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method for predicting the respond of a patient with CLL treated with an agent binding to CD20 comprising Rituximab. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Hogan et al., Witzig et al., Catovsky D, Morrison et al., and Stilgenbauer et al., to the teaching of Golay et al., to predict the response of a patient with specific type of CLL to a treatment with antibody to CD20 (Rituximab) after analyzing the CLL with the abnormalities of chromosome, (deletion of chromosome) because Hogan et al., Witzig et al., and Catovsky D, have shown that different deletions of chromosome result in the abnormal expression of protein involved in B-cell malignancy comprising CLL and CD20 positive CLL cells having 13q14 deletion and Trisomy 12 detected by FISH using probe D13S319 or probe CEP 12, because Catovsky D, has shown that the chromosome deletion at 17p13.1 only results in p53 deletion, and because Morrison et al., and Stilgenbauer et al. have shown analysis of the cells with deletion of 17p13.1 and 11q22.3 detected by FISH using probe **LSI p53 and ATM gene.** One of ordinary skill in the art would have been motivated with a reasonable expectation of success to predict whether a patient can respond to the treatment of Rituximab after knowing the type of chromosome deletion because Golay et al have shown that response to the Rituximab treatment in a CLL patient having malignant leukemic B cells, which express CD20 on the cells.

3. Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrison et al., (US Patent Application Publication, US 2003/0087248, effective filing date Feb, 20, 2001) in view of Fonseca et al., (Leukemia vol 15, page 981-6, June, 2001) and Stilgenbauer et al., (Blood, vol 94, page 3262-4, 1999) and Croce et al., (US Patent, 5928884).

Morrison et al., teach polynucleotide probe **LSI p53**, which is complementary to and hybridize with target resin 17p13.1 of chromosomal 17 and probe **CEP12**, which is complementary to and hybridize with target to 12p11.1-q11 region of chromosome 12 (page 11, table 1). Morrison et al., teach a method of using the combination of probes for detecting cancer that include hybridizing a set of chromosomal

probes to a biological sample obtained from a patients comprising CLL patients (abstract and entire reference).

Morrison et al., do not teach probe for 11q 22.3 and 13q14.3 and a kit containing the probes.

Fonseca et al., teach a probe **LSI D13S319**, which is complementary to and hybridize with target resin 13q14.3 of chromosomal 13.

Stilgenbauer et al., teach **ATM probe** for detecting a deletion in 11q22-q23.

Formation of a kit using known component is within the purviews of one skilled in the art. For example, Croce et al., teach diagnostic kit comprising a DNA probe as an active ingredient (col 44, line 32-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a diagnostic kit comprising the probes, LSI p53, CEP12, taught by Morrison et al., and probes, **LSI D13S319, taught by** Fonseca et al., and **ATM probe taught by** Stilgenbauer et al., for determining the chemosensitivity of CLL patient to treatment. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Morrison et al., Fonseca et al., and Stilgenbauer et al., to the teaching of Croce et al., to make a diagnostic kit containing all the DNA probes for detection of deletion in chromosomes 17p13.1, 12p11.1-q11, 11q 22.3, and 13q14.3 because Morrison et al., have shown a probe **LSI p53 and** CEP12 for detection of deletion of 17p13.1 of chromosomal 17 and deletion of 12p11.1-q11 of chromosomal 12, Fonseca et al., have shown a probe **LSI D13S319**, for detection of deletion 13q14.3 of chromosomal 13, Stilgenbauer et al., for have shown a probe **ATM probe** for detecting a deletion in 11q22-q23 of chromosomal 12 and Croce et al., have shown how to make a diagnostic kit comprising a DNA probe as an active ingredient.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

SHEELA HUFF
PRIMARY EXAMINER